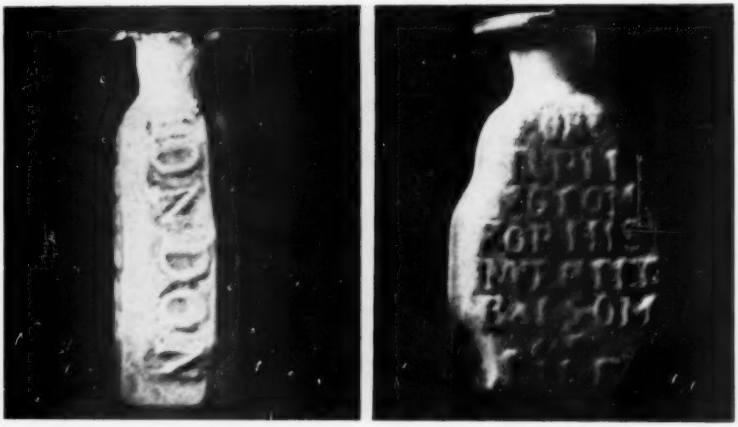
# American Journal of Pharmacy

AND THE SCIENCES SUPPORTING PUBLIC HEALTH



TURLINGTON'S BALSAM BOTTLE FROM
OLD INDIAN SITE IN SOUTH DAKOTA.
(See p. 409)

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# AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825





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## CONTENTS

# E D I T O R I A L

## SUBVERSION OR FREEDOM?

TO many of our friends overseas our present yet continued obsession with witch hunting must be as perplexing as it is depressing to many of us here at home. Americans have always been noted for their respect of fair-play; in fact our devotion to this principle has amazed both our friends and enemies.

That world communism is a continued menace to our way of life cannot be denied. Neither can we meet its challenge only in far away places, important though they may be. We must be constantly awake to the dangers of internal forces of subversion for this is one of the time-tested methods of communism which we have seen at work in Poland, Czechoslovakia and Indo-China. On the other hand, we must not in our efforts to uncover subversion proceed blindly with an unreasonable and unreasoning conviction that all who suggest or propose a philosophy or a procedure contrary to our accepted pattern of social and economic conduct are guilty of subversion and a danger to our American way of life. To do this would be to attempt a regimentation of thought which would preclude all future progress.

Most of us can well remember when the concept of social security or collective bargaining was looked upon as extreme radicalism. Today, even the most conservative Congressman gives both his full support.

The recent report of the Reece Committee on tax-exempt foundations is an example of the degree to which some of our reactionary forces have departed from our American tradition of fair-play. It is also an excellent example of the kind of behavior, now all too common, which is losing favor with many Americans and causing them to alter their political leanings in the direction already quite evident in the 1954 elections.

This committee, at least its Republican majority, has accused the Ford, Rockefeller and Carnegie Foundations of directly supporting subversion. Such accusation it seems is based largely, if not

solely, on the fact that studies financed by these foundations have questioned the propriety and wisdom of certain of our accepted social and economic practices. The suggestion is made by the investigating committee that anyone who is not content with our present way of doing things is un-American and dangerous.

The fact that the committee did not permit responsible officers of these foundations to testify in their own behalf apparently did not itself suggest gross un-American procedure, except to the minority members of the committee.

The United States today faces a terrible and terrifying responsibility in that the free world looks to us for leadership in the world struggle against human misery, slavery and despair. If, in our efforts we ourselves fail to measure up to the standards of truth, fairness and freedom which we hold aloft for the world to see, we and all others dependent on us shall fail in our crusade. In combatting the great threat which is upon us we must not adopt the same evil ways of our enemies. The end can never justify the means.

There is reason to believe that the great body of Americans have passed the uneasy stage concerning this and many similar recent threats to our freedom of thought and expression, and Americans once aroused are a force to be reckoned with. Unless the arch conservatives, super-patriots and demagogues in our midst mend their ways certain of our political parties may have another long wait for their brief day in the sun. For one who himself voted for losing candidates twenty years this is a bleak prospect indeed!

As Americans we must be willing to see customs and practices long established challenged, and listen to the arguments proposed. Ours has been a rapidly changing society with only our basic freedoms, which is the soul of America, kept intact. No threat from within or without is a greater menace than that posed by the possible loss of freedom of inquiry and expression. It is the duty of all Americans to resist at once any attempt to restrict this freedom. The sad plight of those people who chose years ago not to resist such restrictions should be ample proof of our fate, too, should we choose expediency and temporary security rather than defend our heritage of freedom when challenged.

L. F. Tice

# PHARMACY'S CHALLENGE TO THE PROBLEM OF CANCER *

By C. P. Rhoads **

CANCER research has become a major enterprise as a result of public recognition of the progress achieved by determined and extensive scientific effort of the type consequent to the demands of war. Federal and state funds have been appropriated, and private philanthropic organizations created to achieve, by the scientific method, cancer control in man. Sufficient time has now elapsed to permit an evaluation of the progress made. We are satisfied that future gains will depend largely upon the pharmaceutical industry.

The first problem was how to conduct the effort. Whereas all concerned were satisfied that cancer control would only be improved by research, there was no unanimity of opinion as to how this should be arranged, managed and financed. Research to attain a specified end may be conducted in two ways: (1) as a university function co-ordinate with teaching; and (2) in the industrial laboratories, where it is part of a program for the achievement of specific goals.

In industry these goals, understandably, tend to be the ones which are most likely to result in financial gain, since only in this way can industry exist. Unfortunately, the greatest immediate monetary reward does not always result from the accomplishments which are most needed by society. For a pharmaceutical house alone to seek a cancer cure may present fiscal problems, since the outlay required is large and the possibility of achieving its return very slight. It would be difficult to restrict a life-saving drug only to profitable sale.

It was originally concluded, therefore, that the major expense of cancer research would have to be met by public funds, derived either by taxation or solicitation of the citizens. Those in charge decided, furthermore, that these funds should not be expended in the support of work in commercial organizations usually presumed, erroneously, to function *only* for profit. They turned, consequently, to the university laboratories.

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* Presented at the Columbia Bicentennial Conference Oct. 15, 1954.

** Memorial Center, 444 East 68th Street, New York 21, N. Y.

The productive use of the university system in a *program* of research to achieve a definite end, such as the control of cancer, encounters certain limits, however. The university is properly the protector of the freedom of the individual investigator, and the opponent of plan and program except under extreme duress. Furthermore, the primary function of the university is to teach, and teaching is arranged by technical subject and not by the problem to be solved by that subject. Hence university research is organized by subjects, chemistry or physics, and not by the ends to be achieved by their use, such as antibiotics or atom bombs.

Accordingly, the funds made available to the universities for cancer research were expended in the classic divisions in the expectation that, as new information in these subjects developed, some of it would pertain to the cancer problem. This pertinence, it was assumed, would be apparent to all, and would be converted promptly to practical application in cancer control. In actual experience, however, the conversion has been slow. The organization of medical research by technical division is strong, and relatively inflexible. Further, individualism is well established and deeply ingrained. Technique may become an end in itself, and, even though aided by cancer funds, may not always be employed to make an end to cancer. Hence, the management in the university of a *program* to achieve a specific end, such as cancer control, with the necessarily constant shift of emphasis to exploit new observations, can present problems.

The next move was to seek a solution to the problem of conducting cancer research by grants-in-aid in academic subjects, rather than mobilizing subjects to attack cancer. Major grants, sometimes termed "institutional", were made to universities to stimulate internal cooperation of cancer effort without a defined plan of expenditure. It was expected that the chemist, the physicist and the biologist would work together, and since they received support from cancer funds, that they would apply promptly the knowledge thereby achieved to obtaining the goal of cancer progress. This system has been most fruitful in the extension of fundamental knowledge.

Because of the deficiencies of the university as the *only* locus of research to solve the specific problem, several institutes for cancer research have been established. It is already clear that if these are properly organized and staffed, and if they are given continuity of work, with coincidental individual initiative, very considerable progress can be made.

The most important step so far is a new concept opposing the widely held, and stultifying, belief that nothing can be accomplished until some revolutionary new discovery of the most fundamental nature was made. Such cliches as "the riddle of cancer," or "a problem as obscure as the nature of life itself," were, and still are, too frequently bandied about.

Many have come to believe, however, and with good reason, that the hopeless point of view concerning the cancer problem is not entirely justified. Rather, it is now held that there is already more than enough pertinent information, so many obvious and important leads, that the most intense and orderly effort is entirely justified to convert available new knowledge to new applications in the control of cancer in man.

Progress in overcoming the pitfall of the mystery concept of cancer is taking place at an increasingly rapid rate. Most important in this progress is the replacement of this melancholy tradition by the constructive conviction that the cancer cell can be attacked as just another invading micro-organism. It is now seen as one as characteristically different from the normal body cell as is the pneumococcus or the tubercle bacillus, and so potentially as susceptible to selective chemical destruction.

The most impressive evidence in support of this view is at hand in the modern procedures of growing human neoplastic cells outside of the human body. The fact must be recalled that the so-called Koch's Postulates, if fulfilled, have been and still are regarded as conclusive proof that a particular biological entity is causative of a disease process, and must be destroyed if cure is to be attained. These Postulates are three:

1. That the organism be demonstrable regularly in the disease itself.

2. That it be susceptible to culture outside of the body.

3. That it induce the characteristic disease when reinoculated.

They have now been fulfilled for neoplastic disease, as completely as they were for tuberculosis seventy years ago.

Gey has described the sustained culture of cells derived from an original implant of cancer of the human uterine cervix. On purely morphologic grounds, these were presumed to be neoplastic cells, and they now grow so well as to permit their use in many

laboratories as peculiarly suitable media for the cultivation of viruses. More recently, Southam, of our laboratories, and Murray have described the transient cultivation of cells of several types of human neoplasms. Now Moore, in our laboratories, has carried several strains of human cancer cells in pure culture for over a year in bulk.

In all these instances, however, it was extremely difficult to be certain that the cells cultivated are still truly neoplastic cells, still capable of inducing, upon inoculation in man, disease of the type originally explanted. Two crucial experiments have now been performed, which have apparently settled this question.

For many years means have been sought for maintaining human cancer in experimental animals, on a large scale and for prolonged periods, in order to permit reproducible experiments in biology and therapy. Toolan of our institution has recently made a distinguished contribution to this field by devising means for the successful transplantation of human cancer tissue to the irradiated laboratory animal.

More recently, the use of cortisone has been substituted for irradiation and even greater success has been achieved. In the rat or hamster, human cancer tissue will regularly grow and establish definite, though small, deposits of new cells. By the proper choice of animal, and the use of human tumors with a high innate growth potential, so handled as to increase the growth of the neoplastic cells at the expense of the limiting human stroma, four different strains of human neoplasms have been established. Three of epidermoid cancer and one of fibrosarcoma have been in mass transplantation for over one year. An inoculation of 100 mg. of tissue today will yield upwards of 5 grams fourteen days hence. In this way, literally pounds of human cancer are now being harvested each month.

The all-important question still remained, however, of whether cultured cancer cells, so long removed from man, are still human and still neoplastic. A second experiment gave the answer. A patient came under study with widely invasive cancer of the uterine cervix, metastasized to both groins. Since the situation was therapeutically hopeless, it was her desire that she participate in any studies which might be useful to humanity as a whole. Accordingly, she permitted the repeated surgical removal of specimens of cancer tissue for culture and for transplantation to suitable laboratory animals. Both were successful, and substantial growth of the transplants occurred. After several months in culture, when the growth potential and viability of the cancer was well established, the cells were back-

transplanted into the subcutaneous tissue of the patient. Active growth took place of a morphologically true cancer, identical with that removed at biopsy so long before. This is regarded as adequate proof that the neoplastic cells long under artificial cultivation have retained both their human and their neoplastic properties, since ample evidence exists that homologous transplantation of tissue is not possible except to homozygous recipients (identical twins).

We present these experiments as fulfillments of the third of Koch's Postulates, for the neoplastic cell in man. The cells present in and characteristic of the lesion now have been cultivated outside of the human body, both in glass and in animals, and, upon reinoculation in animal and in man, they have reproduced the disease in every detail, including metastasis. With the fulfillment, we submit that an orderly effort to achieve cancer control is justified by the means (chemotherapy) which have already been amply established as effective in controlling disease due to invasion of the body by other forms of parasitic microorganisms.

This conclusion of necessity demands that the experience and the peculiar skills of the pharmaceutical industry be brought to bear upon the problem. Very happily, in our institution the need for this aid had been long seen as inevitable. Accordingly, procedures to achieve it on terms mutually acceptable to the non-profit institution and the industrial organization, had been developed.

In the past it had always been assumed that some incompatibility exist between the two types of institutions. It was thought improper to expend public funds, either donated or derived from taxation, in the support of research in an organization which functions for profit. It is, however, hard to justify logically this point of view, since every research laboratory depends upon industry to supply its equipment and chemicals, and expects industry to make a profit in doing so. This profit obviously must be great enough to cover the cost of further research and development of implements and procedures which can be subject to patent, and so can yield further profits.

Not only can we see nothing improper in close cooperation with industry, but also we can see no possibility of success in achieving our goal of chemicals for the control of cancer without the aid of that industry. With the greatest good will and with the most superior talents, the institution primarily devoted to teaching cannot and does not achieve the same efficiency in the line production of knowledge or of chemicals possible to the highly organized unit devoted primarily

to that particular purpose. Necessary as is the search for knowledge for its sake alone, it is equally necessary that we have organized effort to produce the things to achieve that knowledge.

The scientific work of industry, effort to achieve particular ends, is frequently deprecated on the ground that it pulls scientists away from fundamental interests. It is presumed to limit the investigator's freedom to follow his whim wherever it may lead. This belief has become so widespread that it is accepted in some circles as a fact. Because of this acceptance, serious efforts are presently under way to finance heavily what has been termed "basic research," presumably on the ground that unless such aid is provided, a shortage of basic information will develop. This implies, of course, that those who would have made contributions to basic research if they were permitted, have been forced by economic factors to follow lines of applied investigation which eliminate the possibility of fundamental discovery.

It is well to examine the justification for this widely held belief that there is some incompatibility between research toward a specific end, and the opportunity to make fundamental observations. Even a transient review of the facts appears to indicate that the reverse is true, that basic knowledge often is a by-product of striving for a practical goal.

A substantial part of our fundamental chemical knowledge was derived from the enormous development of industrial chemistry. Polymer chemistry is an example. Our knowledge of immune processes was derived almost entirely from an interest in means for preventing and curing infectious disease. Modern bacteriology is based almost entirely upon the anti-metabolite principles disclosed by the action of sulphanilamide drugs empirically discovered. Basic information concerning carbohydrate metabolism in living organisms is a by-product of the study of diabetes and the search for better means for its control. More recently a whole new field of biologic knowledge regarding cell reproduction and its control has been the product of studies of the neoplastic processes.

There is then good evidence that no incompatibility exists between the pursuit of a specified end and the coincidental acquisition of basic information.

Since we could see no reason for not seeking the aid of the pharmaceutical industry and every reason for doing so, a working plan was developed. It was obvious at the outset that any such plan

must protect at one time the investment of the medical concern and the rights of the public. This means that the ability of industry to patent must be preserved but under such terms as to prevent industry from the holding or exploiting of a discovery essential to the public. Accordingly, a basic contract was developed which has now been in force for many years between our institution and no less than forty-two pharmaceutical laboratories. The terms of this contract are such that both industry and the public are protected. The consequence of the contract has been a constant flow of compounds and information from industry to our laboratories and as constant a flow of new data derived from our work back to industry with suggestions for new procedures. I know of no instance in the past where such a cooperative effort has been instituted to the satisfaction of all concerned. In no instance, to my knowledge, has confidence been violated, and in no instance has the public been anything but the gainer. Certainly without this cooperation, the results so far achieved would have been impossible.

The cooperative program with the pharmaceutical industry has already had important results. They are as follows:

1. A program for the collection, coding and testing of compounds on a variety of neoplasms has been established on an extensive scale.

2. The empiric program has yielded evidence that a number of chemical groups possess some ability to inhibit the growth of animal neoplasms.

3. New basic biological principles have been developed which permit some correlation between the molecular configuration of chemicals and their ability to restrain one or the other type of animal neoplasms.

4. An extensive series of new compounds has been synthesized which provide wholly unique tools for biological studies. Among these, 8-azaguanine and 6-mercaptopurine, prepared by Hitchings of the Burroughs-Wellcome Company, with aid from the Kettering Foundation, are outstanding. The compounds with anti-folic acid activity prepared by the Lederle Laboratories and first used by Farber, have revolutionized cancer research. Azaserine, first isolated from a crude filtrate of streptomycate culture by Parke, Davis & Company, and more recently synthesized, is of particular interest. The congeners of nitrogen mustard, prepared by Parker of the American Cyanamid Company, are the bases of cancer chemotherapy.

It may well be argued that all these sound very well, but as yet there is limited payoff in terms of cancer control in man. This is certainly true and easily understandable. Cancer chemotherapy has progressed through three stages and is now approaching a fourth and specific one. These stages are as follows:

1. The use of escharotic agents such as zinc or arsenic salts, for over a century, to treat localized cancer by the destruction of its component cells. Though long discredited, this is still, in proper hands, a feasible procedure for specific disease as demonstrated by Mohs.

2. Efforts to control cancer of sex-linked tissues by removing the hormonal stimulus to the growth of the normal analogue. The consequence has been the development of androgenic treatment for cancer of the breast and estrogenic treatment for that of the prostate gland. Despite the fact that this type of therapy has improved in effectiveness considerably in recent years, it is not curative nor is it likely to be.

Adequate evidence exists that despite the surprisingly prolonged period of dependence of certain neoplasms on hormonal stimuli, the cells will become autonomous eventually and will grow despite the removal of essentially all the glands of internal secretion. Clearly, for cure something more specific is required.

3. The use of agents which act to stop cellular reproduction in general have some transient effect upon the neoplastic cells. Some neoplasms grow actively, more so indeed than the most actively reproducing normal tissues of the body, that of bone marrow, lymph nodes and intestinal mucosa. The nitrogen mustards and the compounds with anti-folic activity are effective against cancer of these tissues.

4. The most recent stage and a most significant one is the acquisition of knowledge of the specific requirements of particular cells for particular chemicals. This permits the development of antimetabolites which are specifically injurious because of the peculiar characteristics of the cells to be injured. The best example of this compound is 6-mercaptopurine, curative alone or in combination of certain types of animal cancer and useful in treating some types of leukemia in man.

The best example of the specificity of this compound is found in the experiments of Biesele. This worker, studying normal and neoplastic cells dividing at approximately the same rate, showed that 6-mercaptopurine would essentially stop division of the neoplastic units and exert a minimal effect upon that function in the normal ones.

Good evidence is now at hand that 6-mercaptopurine is an important addition to the therapy of animal neoplasms. In combination with azaserine, at levels far below injurious ones, regular and complete destruction of S-180 can be achieved. This is perhaps the first clear demonstration of the ability to cure regularly any form of animal neoplasms. In man the compounds is useful. When used in combination with other agents, it has increased the percentage of children with acute leukemia surviving over one year from twenty-nine per cent to fifty-three per cent. It is, however, not curative and is without effect in neoplasms other than the leukemias.

The minimal usefulness of 6-mercaptopurine in the treatment of human cancer, despite its high degree of effectiveness in some animal neoplasms, has been advanced as evidence of the futility of working in cancer chemotherapy. We hold, however, that it is only a favorable indication. Any ability to achieve specific effects on specific types of cells must depend upon the biological specificity of the cells to be destroyed, on some quality not shared with other types of cellular units. Until now we have had only animal cancer upon which to test on a wide scale the compounds coming from the lines of the pharmaceutical industry. The wholly understandable result has been that we have developed an extensive series of compounds for the cure of animal cancer and they, by virtue of their very specificity, have little effect upon cancer in man. This was really encouraging and not otherwise, since now we have available many types of human cancer growing in tissue culture, on the chorioallantoic membrane of the developing chick embryo, and in cortisonized rats and hamsters. The chemical affinities of those human neoplasms are already under study and have disclosed in preliminary fashion interesting differences from the control tissues employed. Finally, studies of the ability of specific chemicals to restrain the growth of these implants of human cancer have begun with encouraging results.

The cooperative program of the Sloan-Kettering Institute with the pharmaceutical industry in seeking chemical control has been long in development and is broad in scope. It has encountered the difficul-

ties inherent in any program designed to achieve control of an important problem. Real progress has been made, however, the result of a multitude of individual observations. Most important has been the proof acquired for certain new principles of biology which should render some types of cancer as susceptible to control by chemicals as are some types of bacteria to the sulfa drugs. This end has not yet been attained, and many years may elapse before it is attained. Nevertheless, from available evidence it can scarcely be argued that the effort to attain it is unjustified or that the work which has been done has not yielded results in terms of basic information well worth while.

# NEW DRUGS—OLD DRUGS

By Samuel W. Goldstein *

THE earliest records of man's activities indicate his use of plants and other naturally occurring materials for medicinal purposes. During the past one hundred and fifty years, pharmacists and chemists have studied plant drugs, prepared liquid and solid dosage forms from them, isolated their active constituents, learned to synthesize the natural principles and to alter their molecular composition and structure, and to synthesize related and new compounds. Having advanced so far in increasingly rapid stages, the latter part of the first half of the twentieth century witnessed a veritable flood of new medicinals, many of proved therapeutic value, upon the physician, the pharmacist, and the public.

For about three-quarters of a century, Pasteur's observation that some soil constituent detoxified anthrax bacilli was often noted; and the antibacterial action of bacterial growth products such as pyocyanine were reported. But the observations of Fleming in 1929 and the work of Chain, Florey, Abrahams and others with penicillin (1936-1941) and the investigations of Dubos and Waksman with the elaboration products from cultured actinomycetes from soil, unveiled a new field of naturally occurring substances to be isolated, purified, synthesized and altered in the search for better therapeutic agents.

As a result of the knowledge accumulated over many decades, teams of specialists now bridge the period from discovery to clinical trial of new materials and compounds in months rather than decades or years. This accounts for the fact that 75-80 per cent of the drugs most frequently prescribed today are relatively new additions to the materia medica.

## New Drugs from Old

The great advances in organic synthesis have yielded such outstanding masterpieces as the molecular duplication of corticosteroids (cortisone and dihydrocortisone), the finally-achieved quinine synthesis, and, 134 years after the apothecary Sertürner announced his isolation of the vegetable alkali "morphium," Gates and Tschudi ended

* Director of the American Pharmaceutical Association Laboratory, Washington, D. C.

a report in 1952 as follows: "With this, the first synthesis of morphine is complete" (1).

Let us not forget, however, there still remains the transition of the laboratory synthesis of morphine to the pilot-scale production and then commercial manufacture. It would be unwise to suggest that pharmacy students need no longer be taught about opium as the source of morphine and also as the basic source of derivatives such as the new anti-narcotic allylnormorphine.

Atropine was synthesized by Willstatter in 1896, but it was in January, 1954, that the British firm of T. H. Smith, Ltd., announced that it was "the first to achieve large-scale production of tropane alkaloids by an economically sound, synthetic route."

As yet, however, the number of naturally occurring alkaloids and other active principles which have been successfully synthesized on a commercial scale is relatively small.

Relieving the *Atropa* species of the need to supply man with the products of its life's cycle will probably cause only a small stir in the plant world. However, the thoughts of many pharmacists who, though they have not used the information lately, had indelibly impressed in their memories the "official name, habitat, part of plant used, constituents, etc." of *Atropa belladonna*, are probably expressed by D. R. A. Watson (2) in his "Ode to Atropa."

## ODE TO ATROPA

Reflecting on the synthesis of alkaloids of tropine
One wonders if the chemists are really what they might have been.
Considering atropa's done the job since time began,
Without undue distress, great heat, or vacuum-pan.
Is it so commendatory, this effort of mankind,
Starting at the other end, empirically, to find
Succindialdehyde—to nature quite a stranger
(And possibly, to plant life, itself a potent danger)?
Surely 'twere better, more worthy of our setting
As lords of vulgar nature—yet desirable of getting,
To try and understand this plant's intrinsic power
Of manufacturing atropine in berry, leaf and flower
Quietly, secretly, from earth and sun and water,
Ostracised, unloved—except by Borgia's daughter,

One wonders if a greater use, the pupils to dilate,
Would open up our inner eyes, and therefore postulate
A start from Nature's viewpoint—a less esoteric angle?
Might we not succeed the more with less synthetic tangle?

## Old and New Drug Combinations

The advent of the sulfonamides and penicillin was heralded as the beginning of an era of specifics in therapeutics. No more "shotgun" mixtures with vague claims for synergistic combinations. Prescriptions were going to be written for single drugs to treat specifically diagnosed conditions. It appears that some "magic bullets" are again looking more like shotgun shells. Mixtures of sulfas, mixtures of antibiotics, mixtures of sulfas with antibiotics, mixtures with antihistamines, mixtures of the old APC combination with the new drugs: these and many other mixtures appear on prescriptions.

Today, however, more logical reasons, based upon laboratory or clinical evidence, are advanced for prescribed mixtures. Gently hypotensive *Rauwolfia serpentina* from India is associated with its American counterpart, *Veratrum viride*, or with the synthetics, hydralazine or hexamethonium, and synergistic effects have been noted.

The fact that carbomycin, bacitracin, and tyrothrycin are active against the same test bacterium is offered as a possible explanation of the apparent antagonistic effect between carbomycin and the others (3). The fact that polymyxin B and carbomycin are active against different organisms is offered as a possible explanation of the absence of antagonistic effect; but neither do they exhibit synergism under reported laboratory test conditions. The broad-spectrum antibiotic neomycin, and polymyxin, which is effective against *Pseudomonas aeruginosa*, appear to exhibit synergism between them.

Jawetz and Gunnison (4) conclude that no general rules about therapeutic synergism and antagonism can be offered. The same pair of antibiotics can exhibit either effect against different organisms, according to their degrees of sensitivity. It has been noted that bactericidal antibiotics are more likely to show synergism in mixtures, while bacteriostatic antibiotics tend to show only additive effects.

Mixed sulfas exhibit additive therapeutic action and permit lower concentrations of the individual drugs. This is particularly helpful because the renal excretion of the sulfas is individual rather than additive. New sulfas such as sulfisoxazole (Gantrisin) and sulfisom-

idine (Elkosin) are more soluble and can be given in higher doses singly with less danger of crystalluria and renal blocking.

### New Interest in Plant Drugs

Not only do the modern techniques permit the building of unique molecules, as well as those modeled with variations from established compounds; but the new analytical procedures, particularly chromatographic separation, permit more exhaustive and complete studies of old and new plant drugs. Incidentally, the new analytical tool "chromatography" (adsorption of dissolved substances on packed columns of adsorbents and fractional removal or elution by controlled percolation with selective solvents) was first developed by M. Tswett in 1906.

*Veratrum viride* was a drug with uncertain activity and little specific application until refined techniques permitted accurate testing of the hypotensive action of the pure alkaloids. In 1952, Klohs and his co-workers (5) separated neoprotoveratrine and protoveratrine from *V. viride*. Separation of the two alkaloids was accomplished by countercurrent distribution, a modern adaptation of the principle of selective solubility expressed as the partition coefficient between immiscible solvents which has long been utilized in "shake-out" alkaloidal assays.

Steroidal sapogenins have been cited as a plant intermediate in the synthesis of cortical steroids. The sapogenins are present in many plants including the common *Agaves, Yuccas,* and *Dioscoreas,* which flourish in the wild state in the United States and South America. Hecogenin from African sisal juice is transported to a British laboratory for research as an intermediate in the synthesis of cortisone.

*Rauwolfia serpentina,* native to the Himalayan hills of India and used in that country for centuries for insomnia, hypochondria, and insanity, and since 1933 as a sedative and hypotensive agent (6), was introduced into American materia medica in 1952 (7) as the powdered drug for clinical tests in hypertension. In less than three years its therapeutic efficacy, alone and with other hypotensive agents, has been established; an active alkaloidal fraction and the pure alkaloid reserpine have been marketed; and other therapeutic applications such as reduction of anxiety, tension, and nervousness are being reported. It becomes evident that the Indian use of the drug for the treatment of insanity states was sound.

The therapeutic application of the muscle relaxant tubocurarine came as a surprise to many pharmacists who recalled curare as a pharmacognostic curio, interesting only because of its historical use as an arrow poison and its extreme toxicity. Chen and Henderson (8) recently cited the use of the seeds of *Tanghinia venenifera* for the preparation of an ordeal poison, "tanghin," in Madagascar (Virey, 1822). The accused is made to take the poison and is considered to be innocent if he recovers. Application of modern techniques has resulted in separation from those seeds of six crystalline substances which are being tested for their digitalis-like effects.

The beautiful and fragrant oleander, *Nerium odorum*, indigenous to China and India, has been known in China as Chia Tso Tao, and its poisonous property has been recorded. Now the cardiotonic effect of this plant drug and its complex glycosides are being studied.

It is reported (9) that the bark of *Aspidosperma oblongum* contains alkaloids which antagonize the actions of acetylcholine, histamine, barium, and adrenaline, and actually reverse the physiological actions of the latter substance. The alkaloids markedly depress the isolated heart's action and change the electrocardiogram pattern.

Where the many as yet uninvestigated plant drugs and their constituent principles will find their final applications remains for the future to unfold. But it is evident that along with the development of the "miracle" drugs a minor miracle in the form of awakened interest in plant drugs is with us. It appears certain that nature and man's laboratories will continue to collaborate in the development of new and wonderful drugs to aid the pharmacist in his dedicated service to the health and welfare of the public.

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# AN ENGLISH BALSAM AMONG THE DAKOTA ABORIGINES

By Waldo R. Wedel * and George B. Griffenhagen **

MR. Robert Turlington, a merchant of old London, undoubtedly hoped that his "Balsam of Life" would become a successful medicine throughout England when he applied for and received a Kings Royal Patent on January 18, 1744. It is doubtful, however, that he ever dreamed that his patent would wander so far and would perpetuate his name for centuries.

The original Turlington's Balsam of Life contained 27 different ingredients according to the original specifications, and it was claimed as a cure for the stone, gravel, cholic and inward weaknesses if given in doses of 30 to 40 drops (1). According to an article in the *Gentlemen's Magazine* (London) for August, 1748, Turlington's Balsam of Life had already gained for itself a good reputation, and was then selling for one shilling and nine pence per bottle (2).

Soon thereafter, Turlington's Balsam made its appearance among the colonists of America. Dr. George Gilmer, apothecary and physician of Williamsburg, Virginia, announced on September 19, 1751, the importation on the *Duchess of Queensbury* of "a large assortment of Drugs" including Turlington's Balsam (3). The following year (1752) an advertisement appeared in the *Boston Gazette* devoted to Turlington's Balsam which offered this remedy for sale as "prepared and sent by Mr. Turlington the patentee to John Vintenon in Boston" (4). In the Colonies, proprietaries like Turlington's Balsam of Life gained enormous popularity. To the busy settler, with little time and small means, these ready-made and not too high-priced remedies seemed to solve at once all of the problems of medical aid.

It is not known just when Robert Turlington died, but an advertisement which appeared in the *Lloyd's Evening Post* (London) for January 29-31, 1781, noted that "Turlington's Balsam of Life is prepared and sold by Martha Wray, Niece, and Hilton Wray, Successors of Mr. Robert Turlington, the Patentee at the Original Warehouse, the Kings Arms, No. 14, Birchinlane, London, where all persons may be assured of having the Original Genuine Balsam of Life, truly prepared as in his Life-Time, no other person being acquainted therewith." The price quoted indicated that besides the regular 1 shilling, nine pence size, they were also manufacturing a large size at

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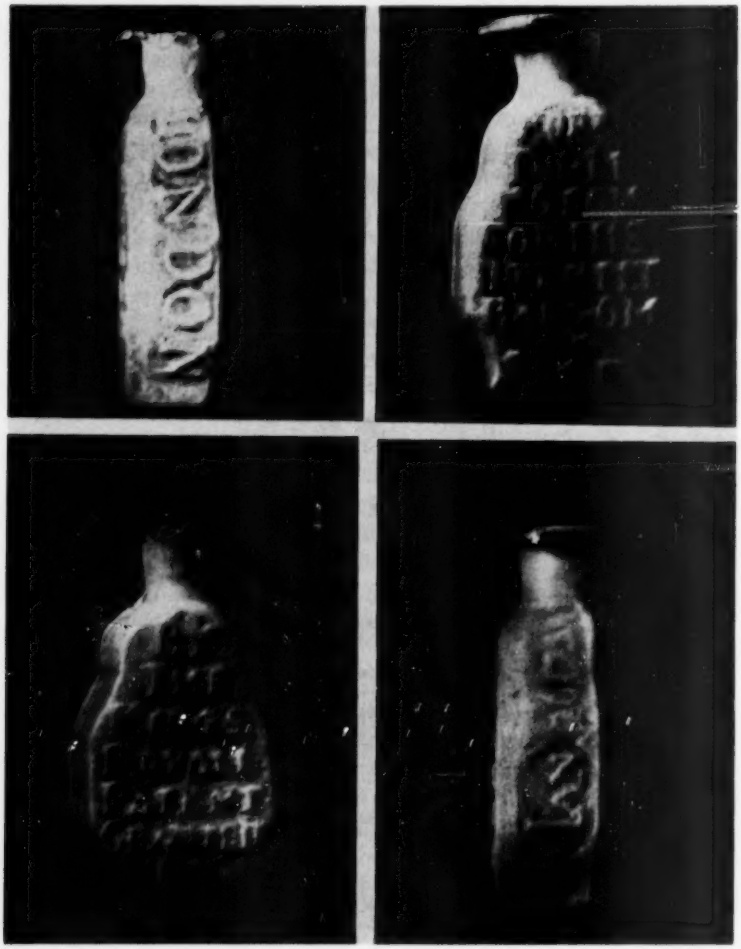
3 shillings six pence. The public was warned that spurious imitations might "be of the worst Consequences if taken" (5).

Following the severance of relations with England, the flow of English patent medicines into the colonies was halted. The apothecary was thus forced to compound his own version of the English counterpart. At the close of the Revolutionary War, the American glass



Turlington's Balsam of Life bottle (all four sides) found in Indian grave at Mobridge, South Dakota

manufacturers began turning out exact duplicates of English patent medicine bottles, even though original proprietaries were again being imported into America.

One early American apothecary, in reminiscing of his apprenticeship days in a Boston drug store in the 1820's recalled that Turlington's Balsam was one of the rather limited group of foreign proprietaries then being imported into Boston. He went on to note that "American imitations of English medicines were extensively sold here (in America) on account of their lower prices. . . . Many, very many days were spent by the writer in compounding these imitations, cleaning the vials, filling, corking, stamping with facsimilies of the English Government stamp, and then wrapping them, with little regard to the originator's rights . . ." (6).

With specific regard for Turlington's Balsam, it is known for example that in 1835 the "Free Will Glass Manufactory of Williamstown (formerly Squawkum), N. J., manufactured Turlington's Balsam vials (7) and George W. Carpenter, Wholesale Druggist of Philadelphia Pa., listed Turlington's vials as one of the "articles which should be purchased by a druggist at the outset of his business," in his catalogue of 1834 (8).

Such a wide variation in formulas of these patent medicines developed that the Philadelphia College of Pharmacy appointed a committee to "reform the recipes for the preparation of some of the Patent Medicines in common use." The committee reported in 1833 "the confusion into which these (Patent Medicines) had fallen for want of some authoritative standard, was productive of some serious evils. . . ." In continuing its report, the committee noted that "it would be desirable in all cases to ascertain the original formula of the medicine, but though many of the recipes claim to be true and genuine, we may place no confidence in them as such. We are persuaded also that the specifications of the patents filed at the Office of Rolls (London) serve only to mislead. An official copy of the specification of Turlington's Balsam of Life will satisfy every member of the board that the medicine either was never prepared thereby or that it would be absurd with our present skill in pharmacy to revert to such an original" (9). The committee thus came up with a standard formula which evolved into what is today known as Compound Tincture of Benzoin.

The popularity of Turlington's Balsam of Life was not restricted to the white settlers and colonists of the Atlantic seaboard. On the contrary, this nostrum was evidently among the early "blessings"

bestowed by advancing American civilization on the Indians of the West. There is mention of it in western Canada as early as 1783 when the Swiss trader Waden, fatally shot by his rival, Peter Pond,

Turlington's Balsam of Life bottle (all four sides)
found on old trading post site of Fort Atkinson, North Dakota

called for Turlington's Balsam to stop the bleeding (10). Later, it appears in the inventories of various fur posts on the upper Missouri River (11). Thus, in an "Inventory of Stock the property of Pierre Chouteau Jr. and Co. U(pper). M(issouri). O(utfit). On hand at Fort Benton 4th May 1851. . . .", "4 doz. (bottles) Turlington Balsam" are listed. In another inventory of May 15, 1851 for Fort Union is an item which reads "3 1/16 doz Turlington @ 50¢." The items listed in these inventories included goods for use at the post as well as for trade with the Indians.

To this documentary material we can now add archeological evidence. Excavations made by a Smithsonian Institution River Basin Surveys expedition in 1952 on the site of the old trading post of Fort Atkinson, North Dakota, (also known as Fort Berthold II) produced two bottles labeled as Turlington's Balsam of Life. Situated some 16 miles southeast of present Elbowoods, North Dakota, this post was founded about 1855 and operated until about 1885. It served a nearby Indian town named Like-a-Fishhook Village, which was established by the Hidatsa and Mandan Indians about 1845. In 1954, additional excavations by the North Dakota Historical Society in the earlier post, Fort Berthold I, brought to light a third bottle identical to those from Fort Berthold II.

That Turlington's Balsam actually came into the hands of the Indians on the Upper Missouri is also shown by archeological findings. In a collection of specimens obtained from a historic Indian burial ground 10 miles north of Mobridge, South Dakota, and out of one of 22 graves opened here for the Smithsonian Institution by Dr. M. W. Stirling in 1923, there is a Turlington's Balsam bottle. This burial ground overlooks a large village site where the principal town of the Arikara Indians stood at the beginning of the 19th century. Lewis and Clark visited the town on their way up the Missouri in 1804, as did Bradbury and Brackenridge in 1811. The site, however, was abandoned in 1833 when Maximilian passed by; thus the period of occupation can be bracketed between 1800 and 1833. The archeological findings clearly show, as is also attested by the contemporary historical documents, that the people buried here were in contact with white men, for besides the Turlington Balsam bottle, numerous other items discovered were unquestionably received in trade with the Whites.

From the Turlington bottles excavated, as well as from the descriptions and/or illustrations reported elsewhere in the literature (12-14), it is obvious that while all are of substantially the same size,

shape, and labeling, a good many variations in detail occur. This is what might be expected from bottles manufactured at various times and by various manufacturers in America and abroad. Characteristically, Turlington bottles are, in form, more or less pear-shaped and laterally flattened, and from 2½ to 3 inches tall. The four sides bear the following inscription, (with slight variations) in raised letters: "(front) By the Kings Royal Patent Granted to (back) Robt Turlington for his Invented Balsom of Life (side) London (side) Jany .... ....." The apparent dates we have seen vary from "Jany 1605" (almost certainly a mis-read date) to "Jany 28 44" to "Jany 26 1954". For an explanation of the latter date see authors' addendum following bibliography.

Curiously enough, on all four bottles we have examined from the upper Missouri valley there appears the word "Balsom" so spelled. None of the references to Turlington's Balsam so far seen by us, including original patent specifications, advertisements, and inventories mis-spells the word Balsam as "Balsom". This consistent mis-spelling may be a means of differentiating English-made bottles from those of American manufacture; or it may be simply the perpetuation of an error started even before bottles of this type were made in this country.

With regard to possible origin of the Turlington bottles uncovered in the excavations mentioned, the bottle found at the South Dakota site (*ca.* 1800-1833) appears to be of English lead glass, while the three bottles from the North Dakota site (*ca.* 1845-1885) are of light greenish cast glass and probably of American make.

It is, of course, impossible to determine from the empty bottles found in the upper Missouri sites whether their original contents were really Turlington's Balsam of Life or, alternatively, one of the "spurious imitations", or adulterated and mis-branded nostrums with which the buyer was so often victimized. On the frontier, and especially in the Indian trade, the code of ethics was a flexible one. Nor do we know how widely Turlington's Balsam was used for trading purposes among the Indians generally. So far as we are aware, Turlington bottles have not been reported from archeological excavations at other sites in the Midwest and West. It may be surmised perhaps that among the upper Missouri Indians, the white man found Turlington's Balsam effective as trading currency no less than as a therapeutic agent for himself. This is, of course, an interesting twist of events, for more often than not, the white settlers called upon the Indians' knowledge of indigenous medicinal plants when their own

supply of medicines ran out or failed its purpose. In any case, this English Balsam—if it actually was such—had truly wandered a long way from home.

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## AUTHORS' ADDENDUM

Since the submission of this article for publication the authors have located a broadside advertising Turlington's Balsam of Life dated ca. 1755-57 in the Historical Society of Pennsylvania, Manuscript Department. At least one paragraph from this original manuscript, which is signed in ink by Robert Turlington, is thought important enough to herein quote in its entirety as follows:

> "Note, In order that no person may be injured in their Health by taking any base Composition, obtruded on the Publick, instead of the Original and truely prepared Balsam is Now altered to the Form described in the Margin of these Bills, on each of which Bottles the following Words are blown in the Glass, viz. on one side, BY THE KING'S ROYAL PATENT GRANTED TO, and on the other Side, ROBERT TURLINGTON FOR HIS INVENTED BALSAM OF LIFE; on one Edge, LONDON, and on the other Edge, JAN$^{y}$. 26, 1754, being the Date of this new Alteration; which I was obliged to make, to prevent the Villainy of some Persons, who buying up my empty Bottles, have basely and wickedly put therein a vile spurious Counterfeit-Sort not having the true Efficacy expected therefrom . . ."

# SELECTED ABSTRACTS

**Rheumatic Fever Therapy With Cortisone, ACTH, and Aspirin.** Houser, H. B., Clark, E. J., and Stolzer, B. L. *Am. J. Med. 16:*168 (1954). A careful comparative study was made of the effects of cortisone, ACTH, and aspirin on the course of acute rheumatic fever in young male adults. A large proportion of the patients was experiencing its first attack of rheu[illegible] was started early. In all, 61 patients cortisone, and 42 received ACTH.

Little difference in the three drugs on the symptoms of rheumatic fever. effect on fever, joint pain, and objectiv ment was greatest with aspirin, with A

Both cortisone and ACTH shorter auriculoventricular conduction although pearance. There was apparently a fav cortisone on heart murmurs, but in so during therapy and persisted. The full the basis of long-term follow-up studie tern was exhibited in each of the three erythrocyte sedimentation rate.

A clinical and/or laboratory rebou the patients in each group after therapy w proposed for this rebound is related t disease. If therapy is discontinued after the clinical symptoms would have subsided naturally, there would be no rebound. The relapse of symptoms subsided spontaneously in all but 8 patients.

Toxicity and/or side effects resulting from the use of the drugs occurred in all of the ACTH- and aspirin-treated patients and in 75 per cent of the cortisone-treated patients. In only four cases were these effects sufficiently severe to require the discontinuation of therapy.

The authors concluded that the over-all effects of each of these drugs leaves much to be desired. Adequate treatment for this disease is not available at present.

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Little difference in the three drugs was observed in their effects on the symptoms of rheumatic fever. However, the rapidity of the effect on fever, joint pain, and objective evidences of joint involvement was greatest with aspirin, with ACTH next greatest.

Both cortisone and ACTH shortened the duration of abnormal auriculoventricular conduction although they did not prevent its appearance. There was apparently a favorable effect of ACTH and cortisone on heart murmurs, but in some cases murmurs appeared during therapy and persisted. The full effect must be evaluated on the basis of long-term follow-up studies. A different response pattern was exhibited in each of the three groups as indicated by the erythrocyte sedimentation rate.

A clinical and/or laboratory rebound occurred in almost all of the patients in each group after therapy was discontinued. One theory proposed for this rebound is related to the natural course of the disease. If therapy is discontinued after the clinical symptoms would have subsided naturally, there would be no rebound. The relapse of symptoms subsided spontaneously in all but 8 patients.

Toxicity and/or side effects resulting from the use of the drugs occurred in all of the ACTH- and aspirin-treated patients and in 75 per cent of the cortisone-treated patients. In only four cases were these effects sufficiently severe to require the discontinuation of therapy.

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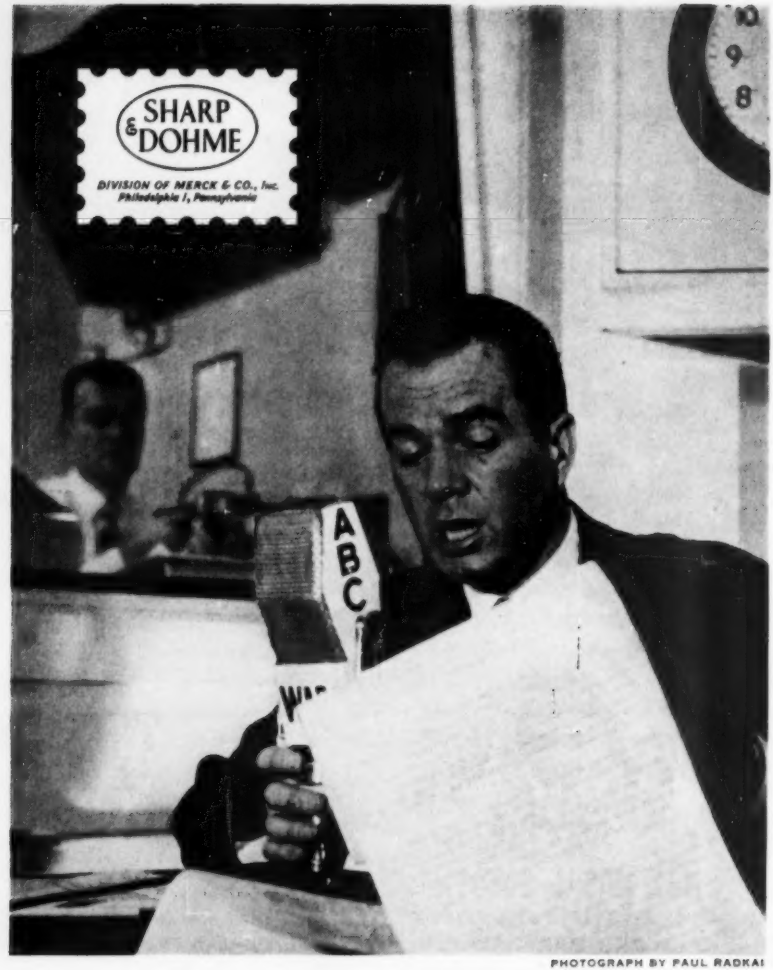


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